Prostatic Intraepithelial Neoplasia: An Overview

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Prostatic intraepithelial neoplasia (PIN) is the most established precursor of prostatic carcinoma. The presence of prominent nucleoli within an existing duct structure is an easy way to identify the disorder. Four main patterns of high-grade PIN (HGPIN) have been described: tufting, micropapillary, cribriform, and flat. In addition to exhibiting similar cytologic features, both HGPIN and prostatic carcinoma are associated with increased incidence and severity with age, and with high rates of occurrence in the peripheral zone of the prostate. HGPIN and prostate cancer share genetic and molecular markers as well, with PIN representing an intermediate stage between benign epithelium and invasive malignant carcinoma. The clinical significance of HGPIN is that it identifies patients at risk for malignancy. With the increased use of extended biopsy protocols, clinicians are more likely to identify HGPIN and less likely to miss concurrent carcinoma. Androgen deprivation therapy decreases the prevalence and extent of PIN, and may play a role in chemoprevention. Preliminary studies suggest that selective estrogen receptor modulators may also prevent the progression of HGPIN to prostate cancer.
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Key words: Prostatic intraepithelial neoplasia (PIN) • High-grade PIN • Prostate cancer • Epidemiology • Biopsy • Repeat biopsy • Androgen deprivation therapy • Chemoprevention

Prostate cancer remains the most common cancer among men in the United States, accounting for more than 200,000 new cases annually.[1] Further, it is estimated that at least one third of men over age 50 years have a latent form of the disease that may eventually develop into prostate cancer. New therapeutic approaches continue to be developed with the goal of intervening during the early phases of the disease in an effort to either reverse or prevent the progression of the neoplastic process. Such prospects have directed research efforts over the

years in efforts to identify precursors of invasive carcinoma.[2]

During the process of malignant transformation, cells gradually evolve from the benign to the malignant phenotype. Premalignant conditions are recognized in many common cancers, including that of the bronchus, skin, urothelium, gastrointestinal tract, breast, and prostate. Prostatic intraepithelial neoplasia (PIN) is a condition "defined by neoplastic growth of epithelial cells within preexisting benign prostatic acini or ducts."[3] Because PIN satisfies almost all the requirements for a premalignant condition, high-grade PIN (HGPIN) is widely accepted as a precursor to prostate cancer.[2,4] Although other prostate lesions may be associated with even higher rates of carcinoma, PIN has been identified as the most likely progenitor of the majority of prostatic adenocarcinomas. Not only is PIN readily identifiable by most pathologists but it is the most likely precursor of adenocarcinoma, making it an ideal candidate for chemoprevention programs. In this review, we will describe PIN and illustrate its premalignant nature. The incidence of PIN on biopsy, as well as of carcinoma on repeat biopsy following PIN, will be discussed in detail. In addition, potential therapeutic strategies will be evaluated.

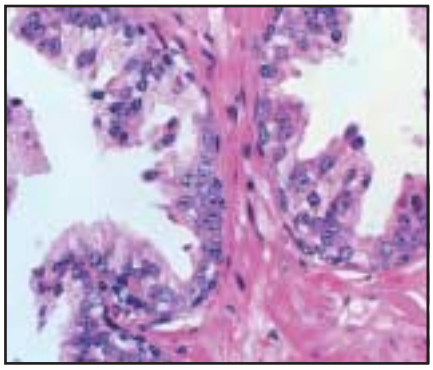


Figure 1. *High-grade prostatic intraepithelial neoplasia: tufting pattern (hematoxylin and eosin, × 400).*

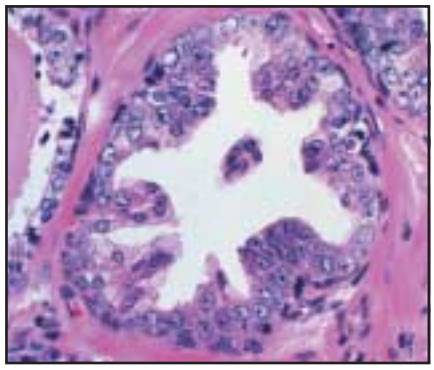


Figure 2. *High-grade prostatic intraepithelial neoplasia: micropapillary pattern (hematoxylin and eosin, × 400).*

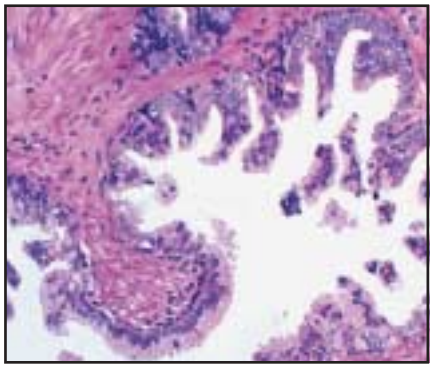


Figure 3. *High-grade prostatic intraepithelial neoplasia: cribriform pattern (hematoxylin and eosin, × 200).*

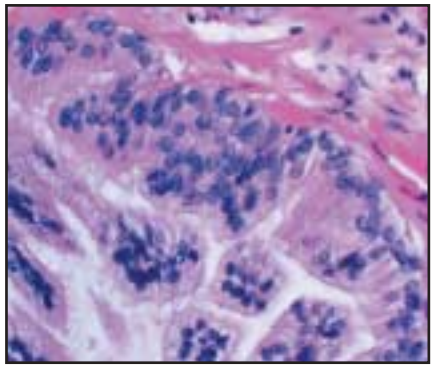


Figure 4. *High-grade prostatic intraepithelial neoplasia: flat pattern (hematoxylin and eosin, × 200).*

History

Historically, there has been a great deal of confusion in the literature on prostatic premalignant changes because of the number of synonyms used to describe these changes. At a consensus conference in 1987, Dr. Gerald Murphy and colleagues endorsed the term "prostatic intraepithelial neoplasia" in keeping with the etymology of a similar condition found in the uterine cervix and in an effort to eliminate the confusion generated by the variety of terms used to describe the condition. Additionally, a grading system for PIN was established, ranging from 1 to 3. Currently, most pathologists do not identify grade 1 PIN, which has been shown to have little or no correlation with malignancy; pathologists do, however, combine grades 2 and 3 into one category (ie, HGPIN). According to several studies,[5] well-trained pathologists have excellent interobserver agreement regarding the identification of HGPIN.

HGPIN Cytologic Changes

The HGPIN lesions depicted in Figures 1 through 4 represent cellular proliferations within preexisting ducts, ductiles, and acinar structures. Cytologic changes in HGPIN, including nuclear and, in particular, nucleolar enlargement, make the lesions indistinguishable from invasive carcinoma on a cell-by-cell basis. The presence of prominent nucleoli within an existing duct structure is an easy way to identify PIN. Cheville and colleagues[6] have described 4 main patterns of HGPIN: tufting, micropapillary, cribriform, and flat. The clinical ramifications of these different patterns seem to be indistinguishable.

In some adjacent tissue sections, there seems to be evidence that HGPIN progressively gains the ability to invade or broach the basal cell layers, thereby transforming into invasive cancer. Basal cell disruption in aciniductals with HGPIN is readily identified by the trained pathologist.

Brawer and associates[7] used high-molecular-weight cytokeratin immunohistochemistry to establish the broaching of the basal cell layer. This method allows for easy differentiation between PIN and invasive cancer.[2,8,9] Bostwick and coworkers[10] have demonstrated that all 4 patterns of HGPIN are associated with the same incidence of microinvasion.

HGPIN and Prostate Cancer

In addition to exhibiting similar cytologic features, HGPIN and prostate cancer share many other similarities, including increased incidence with age and high rates of occurrence in the peripheral zone of the prostate. In contrast, the incidence of HGPIN in the transition zone of the prostate is much less common, occurring in only 2% to 3% of patients.[11,12] It is well established that the volume of PIN has a positive correlation with both pathologic stage and Gleason grade.[13]

HGPIN and prostate cancer share a number of genetic and molecular markers as well, including allelic loss of chromosome 8p12-21,[14] loss of telomere length,[15] and gain of chromosomes 7, 8, 10, and 12.[16] Using cDNA microarray analysis, Calvo and colleagues[17] have identified more than 400 genes that were abnormally expressed in both HGPIN and invasive prostatic carcinoma.

The above findings provide compelling evidence that HGPIN represents an intermediate stage between benign epithelium and the invasive malignant carcinoma, both pathologically and genotypically. Phenotypic changes in differentiation of the cells of PIN and cancer have been established by the expression of different tumor markers. Prostatic acid phosphatase (PAP), prostate-specific antigen (PSA), cytoskeletal proteins, and annexin I protein have all been shown to be progressively lost in PIN relative to benign epithelium.[8,9,18-20]

Tumor Markers

Other markers, such as C-erbB-2 (HER-2/neu) and C-erbB-3 oncoproteins, c-met protooncogene, bcl-2 oncoprotein, several growth factors, nitric oxide synthase, alpha-methylacyl-CoA racemase, glycoprotein A-80, and apolipoprotein D, all have been shown to be upregulated in PIN.[21-24] Henshall and associates[25] recently demonstrated that overexpression of p16INK4A in HGPIN is an independent predictor of prostate cancer relapse, which is the first prognostic marker identified in patients with PIN.

The presence of PIN appears to create changes in the surrounding stroma. Microvessel density has been shown to increase in areas of HGPIN, suggesting that angiogenesis and resulting neovascularity may be affected by factors released from the PIN lesion.[26] The fact that neovascularity is a hallmark of prostatic carcinoma lends further support to the relationship between the 2 entities.

Epidemiology of HGPIN

The incidence of HGPIN on needle biopsy averages approximately 9%, with a range of 4% to 16%. This represents a significant finding because it is estimated that well over 1 million prostate biopsies are performed annually in the United States. As mentioned earlier, the incidence of PIN increases with advancing patient age. In a large study of prostates obtained at postmortem examination in which tissues were analyzed by the whole-mount step section technique, Sakr and coworkers[27] demonstrated that PIN is first reported in men the third decade of life. Most foci of PIN in young men are small and unifocal. With age there are increases in size and grade of PIN lesions.[13]

The prevalence of incidental prostatic carcinoma is quite similar among different radical groups. On the other hand, African American men have a higher incidence of PIN than their Caucasian counterparts.[28] Moreover, Japanese men living in Japan have a significantly lower incidence of HGPIN compared with Japanese men living abroad.[29] In addition, Bostwick[19] has demonstrated that the severity and frequency of HGPIN at postmortem examination are greatly increased in individuals with cancerous prostates compared with those with noncancerous prostates. These findings provide evidence that HGPIN may represent a

Table 1
Estimated Frequency of High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) in the United States

Age (y)	No. US population*	HGPIN (%)
40-49	20,550,000	3,123,600 (15.2)
50-59	14,187,000	3,404,880 (24.0)
60-69	9,312,000	4,404,576 (47.3)
70-79	6,926,000	4,044,784 (58.4)
80-89	2,664,000	1,864,800 (70.0)
Total	53,639,000	16,842,640

*1990 US Census.
Reprinted with permission from Bostwick D et al.[30]

Table 2
Incidence of Isolated High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) in Prostatic Needle Biopsies

Screening Program, Reference	Patient Population	Men, N	HGPIN Incidence (%)
Mettlin et al, 1991[31]	American Cancer Society National Prostate Cancer Detection Project, Roswell Park Memorial Institute, Buffalo, New York	330	5.2
Feneley et al, 1997[32]	Screening population in Gwent, Wales, 1991–1993	212	20
Hoedemaeker et al, 1999[33]	PSA screening study in Rotterdam, The Netherlands	1824	0.7
Urology Practice, Reference			
Lee et al, 1989[34]	Consecutive biopsies of hypoechoic lesions at St. Joseph Mercy Hospital, Ann Arbor, Michigan	256	11
Bostwick et al, 1995[35]	Consecutive biopsies at Mayo Clinic, Rochester, Minnesota	200	16.5
Bostwick et al, 1995[35]	Consecutive biopsies at Glendale Hospital, Glendale, California	200	10.5
Langer et al, 1996[36]	Consecutive biopsies at University of Pennsylvania Medical Center, Philadelphia, Pennsylvania	1275	4.4
Wills et al, 1997[37]	Consecutive biopsies at Johns Hopkins Hospital, Baltimore, Maryland	439	5.5
Feneley et al, 1997[32]	Consecutive biopsies at University College London Hospitals, London, England, 1988–1994	1205	11
O'dowd et al, 2000[38]	Consecutive biopsies at UroCor Labs, Oklahoma City, Oklahoma, 1994–1998	132,426	2.3
Fowler et al, 2001[39]	Consecutive biopsies of men with suspected carcinoma at the Veterans Affairs Medical Center, Jackson, Mississippi, 1992–1998	1050	8.9

Note: Table 2 is restricted to larger studies, with an arbitrary cutoff of 200 or more participants.
PSA, prostate-specific antigen.
Adapted with permission from Bostwick D et al.[30]

marker for biologically significant prostate cancer. The estimated frequency of HGPIN in the United States is illustrated in Table 1.[19,30]

The incidence of PIN varies according to the indication for biopsy. As shown in Table 2, the incidence of HGPIN in screening programs is less than that in contemporary urology practices.[31-39] The clinical significance of PIN lies primarily in the fact that it identifies patients who are at risk for either concurrent or subsequent malignancy.[30,40] Prior studies have correlated the findings of PIN with transrectal ultrasound images.[41]

PIN and PSA Levels

Another area of concern has been whether PIN itself is associated with an elevation in serum PSA levels. We initially showed that in men undergoing simple prostatectomy, the finding of PIN was associated with a high PSA level.[42] Alexander and colleagues subsequently reported that PIN does not appear to increase PSA levels.[43] Of course, the establishment of PIN alone without prostatic carcinoma can only be achieved with whole-mount

step-sectioning of the prostate tissue, which may explain this discrepancy.

PIN Identified On Biopsy

As noted, a major clinical importance of PIN is that it may be predictive of coexisting prostate carcinoma. Since the early 1990s, studies have been conducted of invasive carcinoma identified in men with HGPIN undergoing repeat biopsy. The results of these studies indicate a trend towards decreasing incidence of detecting invasive cancer over time.[44-57]

These data have been recorded during a period of rapid change in our biopsy methodology. Certainly, the use of PSA, ultrasound imaging, and spring-loaded biopsy instruments has revolutionized our diagnostic ability. More importantly, the standard of practice is to perform extended and not sextant biopsies. The likelihood of identifying the coexisting cancer in men with HGPIN is increased by the extended biopsy. Some experts feel that a repeat biopsy is no longer indicated for men with HGPIN only found on an extended biopsy due to the low yield for detecting a cancer.[58] We are more likely to identify PIN and less likely to miss concurrent carcinoma at the initial biopsy experience (see Figures 5 and 6).

Initially, biopsies were performed at specific lesion sites, as identified either by digital rectal examination (DRE) or by transrectal ultrasound. As we recognized that a number of cancers occurred in other sites as well, we adopted randomized biopsy strategies, and have subsequently established more rigorous sampling protocols. As illustrated in Figure 6, when only a few biopsies were obtained, PIN (depicted in the yellow) was identified although other distinct carcinomas might easily have been missed. With more rigorous sampling techniques, as shown on the right side of Figure 6, it would be unlikely that the malignancy (depicted in blue) would have been missed. Currently, it is far more common to find PIN in association with cancer on initial extended biopsy and less likely that cancer will be detected in men undergoing immediate repeat biopsy who have been well sampled and found to have only PIN.

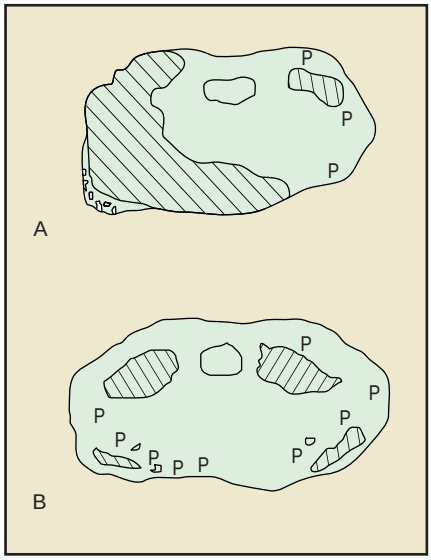
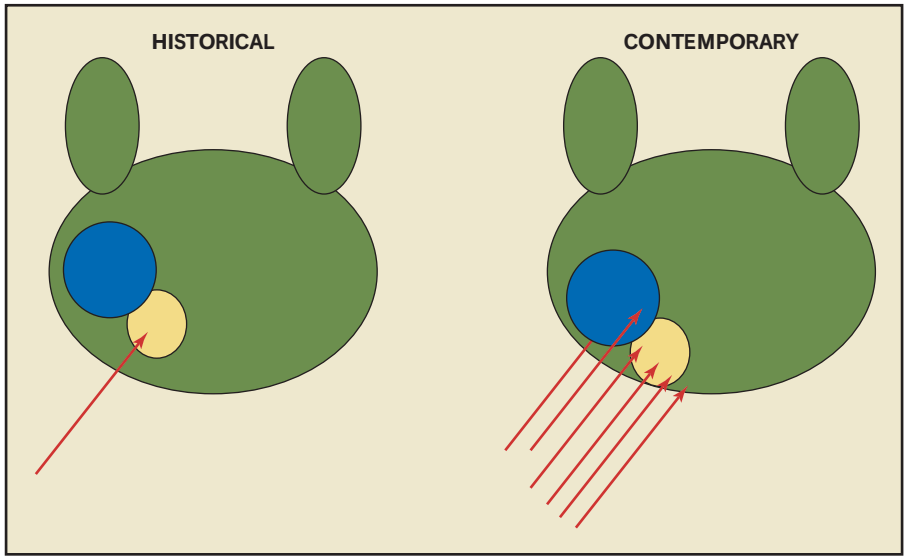


Figure 5. *Representative diagrams of prostate cancer and high-grade prostatic intraepithelial neoplasia (HGPIN) in early 1990s* (A) *and late 1990s* (B). *"P" represents HGPIN. Historically when PIN was found on initial biopsy, repeat biopsy would frequently identify "missed" cancer. Given the size of the lesion, in most contemporary cases, the cancer may more frequently be missed. Figure courtesy of Wael Sakr, MD.*

The identification of HGPIN on prostate biopsy or more rarely on simple prostatectomy specimens mandates careful follow-up because of the increased incidence of concurrent or subsequent development of carcinoma. We recommend follow-up biopsy immediately after the identification of HGPIN only if a sextant biopsy was performed. If only HGPIN is identified on an extended biopsy, we recommend serial monitoring with DRE and PSA measurement. A biopsy is repeated if the PSA progressively rises. Lefkowitz and colleagues[59] recently reported that 25% of men with HGPIN only on extended biopsy will have cancer found on a follow-up biopsy 3 years later. The risk of prostate cancer was independent of PSA level. Although the optimal time for rebiopsy is unknown, there is increasing agreement to repeat the

Figure 6. *Historical biopsy approaches (left) could easily miss invasive cancer (blue) because of undersampling. In modern biopsy approaches (right), with multiple cores being taken, it is unlikely that a concomitant carcinoma in the face of prostatic intraepithelial neoplasia (yellow) will be missed. Reprinted with permission from Bostwick D et al.*[30]



biopsy eventually, even if the PSA level is stable.

Most experts believe that in the absence of prostatic carcinoma, PIN alone is not an indication for invasive intervention. The seemingly inexorable progression into the invasive phenotype, if a man lives long enough,[30,49,53,54,60] has resulted in a number of investigations and increasing interest in using PIN in a chemopreventive framework.

As with prostate cancer and the benign prostatic epithelium, PIN is exquisitely sensitive to the changing hormonal milieu. There is a marked decrease in the prevalence and extent of PIN in men undergoing androgen deprivation therapy prior to radical prostatectomy.[61] Interestingly, 5α-reductase inhibitors such as finasteride appear to have little or no effect on PIN.[62]

A novel antiestrogen agent, toremifene citrate, is currently in phase IIb trials for the treatment of patients with HGPIN. This unique agent is described elsewhere in this supplement. Preliminary results are encouraging.[63] Other possible interventions for the treatment of PIN are presented in Table 3.[31-39]

Table 3
PIN Interventions

- Diet
- Dietary supplements (selenium, vitamin E)
- 5α-reductase inhibitors
- Antiandrogens
- Antiestrogens
- LHRH agonists, LHRH antagonists
- Angiogenic inhibitors
- Differentiating agents
- Chemotherapy

PIN, prostatic intraepithelial neoplasia; LHRH, luteinizing hormone-releasing hormone.

Summary

In summary, the evidence that PIN is a premalignant lesion is compelling. This is reinforced by the fact that both the incidence and severity of disease increase with age and that the prevalence of PIN predates prostate cancer by several years. In addition, at postmortem examination, the frequency and extent of PIN are greater in men with prostate carcinoma than in those without the disease. African American men have the highest risk of developing and dying from prostate cancer. Members of this population also have the highest prevalence of HGPIN in autopsy studies[64] and a greater amount of HGPIN in prostatectomy specimens.[65] As with prostate cancer, PIN is multicentric and is zonally associated with the peripheral zone. Topographic association between PIN and invasive carcinoma has been reported, and microinvasive carcinoma may be seen on sections. ■

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Main Points

- High-grade prostatic intraepithelial neoplasia (HGPIN) follows 4 main patterns: tufting, micropapillary, cribriform, and flat, each of which appears to be useful only for diagnostic purposes.
- On average, the presence of HGPIN is detected in 9% of prostate biopsy specimens.
- A diagnosis of HGPIN is of clinical significance because it is widely accepted as a precursor to prostate adenocarcinoma.
- HGPIN and prostate cancer share genetic and molecular markers, with PIN representing an intermediate stage between benign epithelium and invasive malignant carcinoma.
- Androgen deprivation therapy decreases the prevalence and extent of PIN, and may play a role in chemoprevention.
- Biopsy remains the only certain method of detecting and diagnosing PIN.

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